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Heart Failure: Will There be Any Light at the End of the Tunnel with Stem Cell Therapy?

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THE HEART IS NOT A TERMINALLY DIFFERENTIATED ORGAN

Over the last decade, numerous findings from experimental and clinical studies have challenged the paradigm that the heart is a post-mitotic organ and myocytes are terminally differentiated cells. Recently, two landmark papers have provided compelling evidence in favor of myocardial regeneration. Hsiech et al[1] used a model of transgenic mice to demonstrate that replacement of adult mammalian cardiomyocytes takes place after injury but not during normal aging. Bergmann et al.[2] using an elegant method of determining cardiomyocyte age, showed that even in humans, cardiomyocytes renew at very low rates, with a gradual decrease over the years (1% turnover annually at the age of 25, to 0.45% at the age of 75). Fewer than 50% of cardiomyocytes are exchanged during a normal life span. These findings emphasize the fact that the body's innate ability to repair the heart is inadequate to compensate for a large myocardial injury.

The ideal cell for myocardial regeneration should be easy to isolate and expand in vitro, available as an 'of the shelf' product and with differentiation potential. In addition, safety (no arrhythmias or tumor formation) should be demonstrated before any widespread clinical application. Currently, there is no cell with all these characteristics. However, several cell types, including skeletal myoblasts, bone marrow stem cells, adipose tissue mesechymal stem cells, embryonic stem cells and cardiac residing progenitor cells, have been used experimentally for myocardial regeneration.[3]

SKELETAL MYOBLASTS

Skeletal myoblasts were used very early in cell transplantation studies, due to their availability and ease for cell expansion. However, in clinical trials they have been proven arrhythmogenic and ineffective. In the randomized MAGIC trial[4] the intramyocardial implantation of skeletal myoblasts in patients with ischemic heart disease and ejection fraction <35% failed to improve heart function and the study was terminated early.

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BONE MARROW AND PERIPHERAL CIRCULATING PROGENITOR CELLS

Bone marrow constitutes a source for a variety of progenitor cells like hemangioblasts, mesenchymal and multipotent adult progenitor cells.[5] In a mouse myocardial infarction model, Orlic et al[6] reported that the injected bone marrow c-kit$^+$ stem cells fully differentiated into cardiomyocytes, reduced infarct size and improved myocardial function. However, a subsequent carefully designed experimental study by Murry et al[7] showed that the intramyocardially injected bone marrow stem cells very rarely, if ever, do they differentiate into cardiomyocytes, although they are able to improve myocardial function, presumably through paracrine activity. In an elegantly designed study in transgenic animals, Alvarez-Dolado et al[8] provided evidence that cell fusion of bone marrow derived stem cells with cardiomyocytes was responsible for most of these supposedly 'transdifferentiation' events.

Bone marrow derived stem cells have been tested extensively in clinical trials. In the randomized REPAIR AMI trial,[9] intracoronary administration of bone marrow mononuclear cells was associated with improved recovery of left ventricular contractile function in patients after acute myocardial infarction. Patients with the most severely depressed left ventricular ejection fraction (LVEF) derived the greatest benefit.

Many clinical trials have been completed, assessing the efficacy of the intracoronary infusion of bone marrow derived stem cells or peripheral mononuclear cells in patients with a recent myocardial infarction. In a meta-analysis[10] patients who received intracoronary cell therapy 3 to 7 days after successful reperfusion, had a significant, albeit modest, improvement in LVEF (3.0% increase [95% confidence interval (CI) 1.9 to 4.1]; $p < 0.001$), as well as a reduction in infarct size (-5.6% [95% CI -8.7 to -2.5]; $p < 0.001$).

These encouraging but modest benefits may be explained by the lack of true transdifferention potential of these cells, precluding their engraftment in the heart and synchronization with native cardiomyocytes. Furthermore, the percentage of long term surviving cells in the host myocardium is small.[11]

MESENCHYMAL STEM CELLS

Mesenchymal stem cells constitute another attractive stem cell population. Mesenchymal stem cells (MSCs) are multipotent cells found in several adult tissues. They do not express MHC class II proteins and transplanted allogeneic MSCs can be detected in recipients for a long period after delivery, indicating a lack of immune recognition and clearance.[12]

Schuleri et al[13] injected intramyocardially autologous bone marrow derived mesenchymal stem cells in a swine model, 12 week post-myocardial infarction. MSCs reduced infarct size and increased regional contractility and myocardial blood flow. In a phase 1 clinical study using intravenous administration of allogeneic MSCs derived from healthy donors, in patients after myocardial infarction, Hare et al[14] confirmed the safety and efficacy of this therapy and reported encouraging preliminary findings concerning efficacy.

CARDIAC PROGENITOR STEM CELLS

Several groups have reported the existence of resident cardiac stem cells that are able to differentiate into the main cardiac cell types (cardiomyocutes, smooth muscle and endothelial cells). Messina and colleagues first demonstrated that cardiac progenitors cells (CPCs) could be grown directly from cardiac tissue and further enriched after going through a tissue culture step that involved the formation of spherical aggregates, called cardiospheres.[15] Extensive research in Eduardo Marban's lab at Johns Hopkins University further advanced this method towards clinical translation, by developing a technique for expanding cells from these cardiospheres, in order to yield a sufficient amount of cardiosphere-derived cells (CDCs) with cardiogenic properties. Human CDCs injected into the border zone of myocardial infarcts in immunodeficient mice engrafted and reduced infarct size.[16] Using *in vivo* imaging techniques[17] and reporter genes the same group showed that only a fraction of the injected cells survive after the first few days following their delivery to the myocardium. In addition, they demonstrated that augmenting CDC retention resulted in greater improvement in cardiac function[18].

Johnston et al reported that CDCs administered via the intracoronary route were effective in ameliorating left ventricular remodeling after myocardial infarction, in a porcine model.[19] These encouraging data from the preclinical studies with CDCs, lead to a phase I clinical study (NCT00893360), which investigates the feasibility and safety of intracoronary administration of autologous CDCs, in patients with decreased LVEF after myocardial infarction. Efficacy will also be assessed as a secondary end point.

INDUCED PLURIPOTENT STEM CELLS

Embryonic stem cells (ES) are the only cell type that fulfills the criteria of a real stem cell: pluripotency and self-renewal. However, their clinical application encounters severe obstacles, including ethical issues regarding their isolation from embryos. One way to circumvent these issues is to generate pluripotent cells directly from somatic cells. Takahashi et al[20] described a method where over-expression of four transcription factors, characteristic of ES cells, in mouse fibroblasts lead to the generation of ES-like pluripotent stem cells. The cells, named induced pluripotent stem (iPS) cells, could

be differentiated into cells of all three germ layers including cardiomyocytes. Recently, human iPS cells were successfully differentiated into cardiomyocytes in vitro.[21] However, the development of methods for directing differentiation of these cells towards the desired cell line is still needed, in order to eliminate the danger for teratoma formation.[21]

CONCLUSION

Cardiac regeneration using stem cells emerges as a novel treatment option for heart failure. Clinical applications have reported encouraging but modest favorable results, concerning cardiac functional recovery. However, many issues need clarification. The most appropriate cell type, the optimal number of injected cells and time for cell delivery, as well as the mode of cell function (differentiation or paracrine mechanism) remain to be elucidated. Furthermore, ways to improve cell survival and long term engraftment are being sought, in an effort to enhance the regenerative capability of the cells. A substantial amount of basic, translational and clinical research is still needed, in order to take advantage of the full therapeutic potential of stem cell treatments for heart failure.

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